Current Concepts of Cerebrovascular Disease — Stroke

Acute Medical Therapy of Strokes

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THE BEST treatment of the various stroke syndromes is their prevention, a realistic possibility attested to by the declining incidence of strokes by nearly one-quarter over the past three decades. This gratifying trend is due in large part to the control of hypertension (blood pressure over 160/90 to 95 mm Hg in adults), which not only triggers intracerebral hemorrhage but also contributes to atherosclerosis-related strokes and their recurrence. Whether intervention in other risk factors associated with strokes, such as hyperlipidemia, predictably decreases stroke occurrence is uncertain, but moderation as a good health habit appears prudent until more precise risk markers can be identified.

Since “stroke” is a generic term applied to acute neurological deficits attributable to vascular disease, the pathology should be identified, such as occlusion by thrombus or cardiac emboli, or rupture, as in hypertensive bleeds or with congenital (“berry”) aneurysms. Although it is preferable to establish the diagnosis since it will dictate both therapy and prognosis, even in experienced hands as many as 25% of the strokes cannot be easily classified because of insufficient clinical or laboratory data. Nonetheless, a reasonably accurate diagnosis can be made at the bedside by analysis of the history and the examination in the majority of patients.

Variety of Stroke Syndromes

Thrombotic or thromboembolic strokes due to atherosclerotic disease of either the extracranial or intracranial arteries account for approximately 75% of the strokes in the U.S. Future issues of this journal will detail the clinical aspects of thrombotic strokes and their various manifestations.

Intracerebral hemorrhage is primarily due to hypertensive vascular disease, and the clinical manifestations of bleeding into the five anatomical areas of the brain display characteristic neurological findings (also to be a topic of a future issue). The five areas are the putamen (deep basal ganglia nuclei, accounting for 60% or the majority of strokes), cortical or lobar white matter (10%), thalamus (10%), pons (10%), and cerebellum (10%). Differential diagnosis is important because patients with white matter (or lobar) and cerebellar hemorrhages who have symptoms of increased intracranial pressure (such as obtundation or stupor) can be saved by neurosurgical decompression with the expectation of viable recovery.

Embolism of cardiac origin is frequently presumed because a potentially offending cardiac process, such as atrial fibrillation, recent myocardial infarct, or a prosthetic valve, is associated with a stroke syndrome. Newer techniques to detect the presence of platelet hyperaggregability and hypercoagulability, in addition to two-dimensional echocardiography to identify cardiac thrombi or a prolapsed mitral valve, offer promise of better pathological identification of the embolic source. This topic plus the apparent clinical efficacy of immediate anticoagulation with heparin to prevent re-embolization in patients showing no brain hemorrhage will also be reviewed subsequently.

Subarachnoid hemorrhage (SAH) due principally to congenital or berry aneurysms is a neurosurgical problem since ligation or extirpation is the only definitive therapy. Two major complications of SAH are re-bleeding and vasospasm. Rebleeding is due to fibrinolysis which dissolves the protective thrombus, but the value of antifibrinolytic agents, such as epsilon-amino caproic acid (Amicar), is uncertain since the data are conflicting. Vasospasm is more problematic because the etiology is less well understood but is probably multifactorial, and no definitive treatment has surfaced although the use of calcium channel blockers has a persuasive rationale.

Asymtomatic carotid bruit remains a controversial and hotly debated subject between those who recommend endarterectomy for an offending stenotic or ulcerating lesion in the carotid and those who support a conservative view. A subsequent review of this topic will compile and analyze the various studies on this subject along with the role of noninvasive testing for carotid disease. In the final analysis this area in particular requires the physician’s exercise of clinical judgment in deciding risk/benefit because the problem must be individualized.

Philosophy and Ethics of Stroke Therapy

The effort and cost expended in stroke therapy must be balanced against the likelihood of improving the patient’s quality of survival. A large percentage of strokes are encountered in the elderly with massive deficits and stupor, and prolonging life with resuscitative and support systems is not the objective of therapy. However, all efforts should be made to treat the underlying cause of stroke in patients with mild to moderate deficits since viable recovery can be attained, particularly for the 20% under the age of 65 who display mild deficits. The majority of this group will return to work or their antecedent physical activities.

Medical Treatment for Acute Strokes

Acute therapy can be divided into three major classes: (1) anti-edema therapy including steroids and
dehydrating agents such as mannitol, urea, and glycerol; (2) anticoagulation with heparin and coumadin and antiplatelet aggregation drugs such as aspirin and persantine; and (3) therapies to improve cerebral blood flow and metabolism.2-7

Anti-Edema Agents

The rationale for using anti-edema agents is twofold: (1) brain swelling may impair blood flow, particularly to microcirculation, and (2) excessive brain swelling will cause herniation. The two common forms of herniation are uncal (herniation of the temporal lobe through the opening over the tentorium cerebelli causing deepening stupor, third nerve paralysis, and increase in hemiparesis) and tonsillar herniation (respiratory failure, quadriaparesis). With these types of herniation death is imminent, and shrinkage of brain should be undertaken.

Steroids such as dexamethasone are effective in reducing brain swelling due to “vasogenic” edema, which is seen primarily with brain tumors but may occur with intracerebral hemorrhage several days after the stroke. As the term “vasogenic” implies, the swelling is believed to be due to a “leakiness” of vessels and occurs at least 24 hours after the stroke. Steroids can be instituted if there is a suspicion of “vasogenic” edema such as breakdown of the blood-brain barrier by brain scan. The dosage is 4 mg dexamethasone every 6 hours intravenously or orally for one week tapering to discontinuation. Routine use of steroids is discouraged and should not be considered without evidence of breakdown of the blood-brain barrier.

Mannitol, urea, and glycerol produce a sudden increase in osmolality of the serum which “draws” free water from the brain. The effect is short and temporary and should restrict herniations when emergency surgery is contemplated. Mannitol is the drug of choice as a dehydrating agent. A dose of 250 cc of 20% solution of mannitol can be given rapidly.

Dehydrating agents should be used only if surgery is seriously contemplated. In a herniating “stroke” patient brought to the hospital without adequate history, a surgically operable lesion such as a subdural hematoma cannot be excluded. Under these circumstances mannitol is indicated in order to obtain a CT scan or cerebral angiogram to determine the cause of herniation.

Anticoagulation and Antiplatelet Aggregation Drugs

Intra-arterial thrombus formation and platelet aggregation are two mechanisms responsible for the majority of stroke syndromes. These include thrombotic or thromboembolic strokes, TIA’s, RIND’s, progressing strokes, and embolic strokes of cardiac origin. The rationale for anticoagulation is to retard the thrombotic process. Antiplatelet aggregation drugs restrict the platelet plug size, purportedly the cause of most TIA’s and RIND’s.

Anticoagulation has been recommended for transient ischemic attacks of brain (TIA’s), so-called reversible ischemic neurological deficits (RIND’s), progressing strokes or strokes-in-evolution, and embolic strokes of cardiac origin. Because of questions of research design and interpretation of data, reservations on the value of anticoagulation for TIA’s and RIND’s have been raised. Less controversial is the use of anticoagulation in progressing strokes and embolic strokes of cardiac origin where therapy reduces the chance of neurological worsening and recurrence of emboli, respectively. The controversy over the value of anticoagulation in TIA’s has been somewhat subbed by recent evidence that the safer antiplatelet aggregation drug, aspirin, will reduce the incidence of strokes.

Blood coagulation is triggered by two pathways: “intrinsinc,” because circulation coagulating factors are activated, and “extrinsic,” because noncirculating coagulant tissue factors are introduced into the circulation. With the various stroke syndromes the intrinsic pathway is believed to be activated by exposure of the basement membrane in ulcerating atheromas. The intrinsic coagulation pathway begins with the serial activation of the various factors beginning with Factor XII. This factor serially activates XI, IX, VIII, and X. With Factor V, a regulator protein, prothrombin or Factor II is converted to thrombin, which in turn converts fibrinogen to the soluble fibrin monomer and fibrinopeptides. These in turn, in the presence of Factor XIII, form a stable, insoluble fibrin polymer, the end product of coagulation.

Heparin, a sulfated mucopolysaccharide, achieves immediate anticoagulation by its activation of plasma antithrombin. Coumadin achieves anticoagulation by inhibition of the four vitamin K-dependent clotting factors (II, VII, IX, and X). However, drug interactions are important to consider: for example, salicylates potentiate while barbiturates inhibit the activity of coumadin.

Acute, short-term use of heparin intravenously for approximately seven days followed by chronic therapy with coumadin for three to six months is recommended for (1) progressing strokes or stroke-in-evolution (wherein neurological deficits increase over a period of several hours but not because of intracerebral bleeding), and (2) strokes due to cardiac emboli, such as atrial fibrillation and myocardial infarction, unassociated with intracerebral bleeding. Because antiplatelet aggregation drugs appear to be effective in reducing strokes associated with TIA’s and RIND’s, anticoagulation is not recommended as medical therapy unless symptoms continue.

Heparin is given intravenously, preferably by continuous infusion, at the rate of approximately 1,000 units per hour using IVAC after a 5,000 unit bolus. The partial thromboplastin time (PTT) should be kept at approximately 2 to 2½ times control (80 to 100 seconds). For chronic therapy 5 to 10 mg of coumadin daily can be commenced soon after starting heparin. Since it takes 4 to 5 days to reach a stable plateau, prothrombin time maintenance at 1½ to 2 times control can be adjusted after that time.

Platelets are derived from bone marrow megakaro-
cytes and have a life span of approximately 8 to 10 days in the circulation. The normal platelet count varies between 175,000 and 350,000/cmm. Hemostasis prevents exsanguination and occurs in four sequential reactions; (1) adhesion, (2) release reaction, (3) aggregation, and (4) consolidation. Adhesion refers to the sticking of platelets to foreign nonendothelial surfaces such as the basement membrane of an ulcerating atheroma. The platelets then undergo a "release reaction" in which they discharge a number of intracellular compounds, including adenosine diphosphate (ADP), prostaglandin (thromboxane A₂), beta-thromboglobulin, serotonin, proteolytic enzymes, and permeability factors. As a result of the secretion of ADP and thromboxane A₂, other platelets aggregate to the initial platelets to form a platelet plug. Meanwhile, exposure of Platelet Factor 3 (PF₃) encourages coagulation by activation of Factor XI and XII.

Antiplatelet aggregation drugs inhibit aggregation primarily by inhibiting the "release reaction." Aspirin and sulfinpyrazone (Anturane) accomplish this by inhibiting cyclo-oxygenase, the first enzyme in converting arachidonic acid (C₂₀₋₄) to prostaglandins. On the other hand, dipyridamole (persantine) inhibits ADP release by inhibition of phosphodiesterase, which increases intracellular cyclic AMP.

Recent evidence shows that arterial walls synthesize a prostaglandin called prostacyclin, or PGI₂, which inhibits adhesion and aggregation of platelets, and that large doses of aspirin (12 to 14 tablets a day) will inhibit this "protective" prostaglandin synthesis. Accordingly, low-dose aspirin (one or two tablets daily) is being recommended to inhibit platelet generated aggregants while preserving arterial wall antiaggregate prostacyclin.

For antiplatelet aggregation, we recommend a combination of aspirin and dipyridamole since the two should affect both the prostaglandin and cAMP systems for a synergistic impairment of aggregation. Although the combination is currently being evaluated and, therefore, its efficacy is unproven, an apparent value of the two drugs has been demonstrated with emboli associated with cardiac prostheses. A low dose is recommended, namely, one aspirin a day plus dipyridamole 50 mg three times a day.

**Therapy to Improve Cerebral Blood Flow**

Although the use of "vasodilators" to increase blood flow to an ischemic area has theoretical justification, their clinical value has not been proven. The compounds include papaverine, carbon dioxide, dihydroergonovine, nyridrin, cyclandelate, hexobendine, betahistine, and beta-adrenergic blocker.

Since delivery of oxygen to ischemic tissue is not enhanced, oxygen therapy is of no benefit unless arterial oxygen is reduced.

As with vasodilators, vasopressor therapy has been used to increase blood to an ischemic area on the theory that with impaired "autoregulation" in strokes, cerebral blood flow becomes proportional to the "perfusion pressure" (defined as the systemic blood pressure minus venous pressure). This therapy has not been assessed in a controlled fashion, but there have been anecdotal reports of benefit. Although a prospective study is necessary, vasopressor therapy should be considered in normotensive ischemic stroke patients, especially those who develop neurological deficits during cerebral angiography. It is recommended that the diastolic pressure be raised 10 to 20 TORR with intravenous Leovophed or dopamine.

Reduction of blood pressure in strokes should be avoided because it can increase the neurological deficits. The only exception is in hypertensive encephalopathy, and while antihypertensive therapy in this condition is urgent and lifesaving, marked reduction of blood pressure should be avoided since it can cause ischemic infarction.

Hyperventilation therapy to reduce PaCO₂ has no place in stroke therapy.

Although evidence from experimental models of both global and focal brain ischemic injury shows that barbiturates will protect against damage, no such evidence exists for humans.

**References**
